PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE
in its capacity as elected Office

Date of mailing (day/month/year) 23 February 2001 (23.02.01)	
International application No. PCT/EP00/05722	Applicant's or agent's file reference HF 2097/061/PCT
International filing date (day/month/year) 21 June 2000 (21.06.00)	Priority date (day/month/year) 09 July 1999 (09.07.99)
Applicant CASTALDI, Graziano et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:
21 December 2000 (21.12.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was
[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer F. Baechler
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

EP0005722

Form PCT/IB/331 (July 1992)

N1

PATENT COOPERATION TREA

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
HF 2097/061/PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 00/ 05722	21/06/2000	09/07/1999
Applicant		
NICOX S.A.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 2 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. —

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/05722

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C203/04 C07C201/02 C07C67/14 C07C69/90

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 16405 A (NICOX SA) 9 May 1997 (1997-05-09) cited in the application page 14 -page 15	1-4
A	WO 92 01668 A (ITALFARMACO SPA) 6 February 1992 (1992-02-06) page 5, line 19 - line 29; claim 1	1
A	WO 95 09831 A (NICOX LTD) 13 April 1995 (1995-04-13) claims 15,16	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search
9 November 2000

Date of mailing of the international search report
22/11/2000

Name and mailing address of the ISA
European Patent Office, P.B. 5818 Patentlaan 2
NL 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer
Bonnevalle, E

1

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/05722

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9716405 A	09-05-1997	IT MI952263 A	30-04-1997
		AT 193883 T	15-06-2000
		AU 709338 B	26-08-1999
		AU 7495096 A	22-05-1997
		BR 9611175 A	30-03-1999
		DE 69608916 D	20-07-2000
		EP 0871606 A	21-10-1998
		ES 2148808 T	16-10-2000
		HU 9802986 A	28-04-1999
		JP 11514636 T	14-12-1999
		SI 871606 T	31-08-2000
		US 6040341 A	21-03-2000
WO 9201668 A	06-02-1992	IT 1243367 B	10-06-1994
		AT 118478 T	15-03-1995
		AU 8097491 A	18-02-1992
		CA 2087442 A	27-01-1992
		DE 69107459 D	23-03-1995
		DE 540544 T	23-09-1993
		DK 540544 T	26-06-1995
		EP 0540544 A	12-05-1993
		ES 2056783 T	16-10-1994
		GR 93300079 T	31-08-1993
		HU 63374 A	30-08-1993
		HU 213405 B	30-06-1997
		NO 930215 A	22-01-1993
		US 5589490 A	31-12-1996
		US 5366992 A	22-11-1994
WO 9509831 A	13-04-1995	GB 2283238 A	03-05-1995
		IT 1269735 B	15-04-1997
		AT 168986 T	15-08-1998
		AU 678063 B	15-05-1997
		AU 7809294 A	01-05-1995
		BR 9407749 A	12-02-1997
		CA 2173582 A	13-04-1995
		DE 69412109 D	03-09-1998
		DE 69412109 T	21 -1999
		DK 722434 T	16-11-1998
		EP 0722434 A	24-07-1996
		ES 2120070 T	16-10-1998
		HK 1004916 A	11-12-1998
		HU 74446 A	30-12-1996
		JP 9503214 T	31-03-1997
		RU 2136653 C	10-09-1999
		SI 722434 T	31-12-1998
		US 5700947 A	23-12-1997
		US 5780495 A	14-07-1998
		AT 184589 T	15-10-1999
		AU 702662 B	25-02-1999
		AU 2215695 A	29-11-1995
		BR 9507634 A	23-09-19
		CA 2190087 A	16-11-1995
		DE 69512232 D	21-10-1999
		DE 69512232 T	24-02 0
		DK 759899 T	20-12-1999
		WO 9530641 A	16-11-1995
		EP 0759899 A	05-03-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 00/05722

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9509831 A		ES 2139199 T	01-02-2000
		GR 3032078 T	31-03-2000
		HU 75961 A	28-05-1997
		JP 9512798 T	22-12-1997
		SI 759899 T	31-12-1999
		US 5861426 A	19-01-1999

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SAMA, Daniele.
SAMA PATENTS
Via G.B. Morgagni, 2
I-20129 Milano
ITALIE

SAMA PATENTS
26 MAR. 2001
RECEIVED

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 22.03.2001
Applicant's or agent's file reference HF 2097/061/PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/05722	21/06/2000	09/07/1999

Applicant
NICOX S.A. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Roche, S Tel.+49 89 2399-8031

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
HF 2097/061/PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/05722	21/06/2000	09/07/1999
International Patent Classification (IPC) or national classification and IPC		
C07C203/04		
Applicant		
NICOX S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21/12/2000	22.03.2001
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Heibl, C Telephone No. +49 89 2399 8331

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/05722

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-11 as originally filed

Claims, No.:

1-7 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-7
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-7
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 1-7
	No:	Claims

2. Citations and explanations
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Section V----------

(The numbering of the prior art documents (D1,D2..) cited hereinafter corresponds to the order in which they are mentioned in the International Search Report.)

The problem to be solved by the process of the invention can be seen in providing an improved process for producing the nitroxy derivatives of formula I (see claim 1) on industrial scale without the drawbacks of the related prior art (expensive nitration agents, undesired side reactions etc.).

The underlying problem is solved by a process as claimed which is essentially characterized by firstly producing the salicylic hydroxymethyl-phenyl ester I-B by reaction of the salicylic acid halide I-A with hydroxybenzylalcohol (step a)) and subsequently nitrating the so obtained hydroxymethyl derivative I-B by using a nitration mixture comprising steaming nitric acid and a further inorganic acid or an organic acid anhydride (step b)).

The process of the present invention is neither anticipated nor rendered obvious by the available prior art documents.

Indeed, D1, which is also mentioned in the present description (see page 1), teaches to react acetylsalicylic acid chlorid with 3-hydroxybenzylnitrate which has been obtained by reaction of bromomethyl phenol with $AgNO_3$ as nitrating agent, cf. D1 pages 12-15.
D2 discloses the same reaction principle, viz. the reaction of a benzoic acid halide derivative with pre-formed nitric ester of the general formula HO-Y-ONO_2 (or H_2N-Y-ONO_2) with a functional reactive derivative of substituted benzoic acids, cf. D2, page 5, lines 19-29. Alternatively, the nitration of a bromoethyl benzoic acid ester employing silver nitrate is described in Example 8.
D3 discloses a method for producing nitric ester derivatives which comprises the steps of converting a hydroxyalkyl group into the corresponding alkyl halide group and subsequently nitrating the halo derivative with $AgNO_3$, cf. D3, claims 15 and 16.

The subject-matter of claims 1-7 is thus considered to meet the requirements of Art. 33 (2)-(4) PCT.

Re Section VIII----------

Claim 1: The passage defining preferred embodiments (cf. "*preferably in (I) ...*") should be made the subject of an independent claim.

Claim 2 requires that the base be "*an inorganic or organic base*". It would appear that another possibility does not exist. The claim therefore does not seem to provide technical information in addition that of claim 1.

HF2097/061/PCT

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 January 2001 (18.01.2001)

PCT

(10) International Publication Number
WO 01/04082 A1

(51) International Patent Classification[7]: C07C 203/04, 201/02, 67/14, 69/90

(21) International Application Number: PCT/EP00/05722

(22) International Filing Date: 21 June 2000 (21.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI99A001517 9 July 1999 (09.07.1999) IT

(71) Applicant *(for all designated States except US)*: **NICOX S.A.** [FR/FR]; 45, avenue Kléber, F-75116 Paris (FR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **CASTALDI, Graziano** [IT/IT]; Via Livia Gallina, 5, I-28072 Briona (IT). **OLDANI, Erminio** [IT/IT]; Via San Massimo, 82, I-20018 Sedriano (IT). **RAZZETTI, Gabriele** [IT/IT]; Via G. Puccini, 60, I-20099 Sesto S. Giovanni (IT). **BENEDINI, Francesca** [IT/IT]; Via Padova, 286, I-20100 Milano (IT).

(74) Agents: SAMA, Daniele et al.; Sama Patents, Via G.B. Morgagni, 2, I-20129 Milano (IT).

(81) Designated States *(national)*: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA.

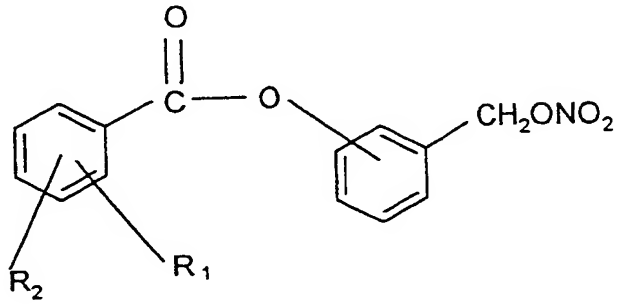
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: A PROCESS FOR OBTAINING (NITROXYMETHYL)PHENYL ESTERS OF SALICYLIC ACID DERIVATIVES

WO 01/04082 A1



(I)

(57) Abstract: A process for obtaining (nitroxymethyl)phenyl esters of salicylic acid derivatives of formula (I) wherein R_1 is the $OCOR_3$ group characterized in that it comprises the following steps: a) reaction of a halide of a salicylic acid derivative with hydroxybenzylalcohol in the presence of a base; b) nitration of the obtained product in anhydrous conditions by a mixture of nitric acid with a different inorganic acid, or an organic acid, or an anhydride of one or two organic acids; c) recovery of the final product.

A PROCESS FOR OBTAINING (NITROXYMETHYL)PHENYL ESTERS OF SALICYLIC ACID DERIVATIVES.

* * * *

The present invention relates to a process for obtaining (nitroxymethyl)phenyl esters of salicylic acid derivatives.

It is known in the prior art that the (nitroxymethyl)phenyl esters of the salicylic acid derivatives can be prepared by various synthesis processes. In the patent application WO 97/16405 the reaction of the acyl chloride of the acetylsalicylic acid with (nitroxymethyl)phenol is described. The (nitroxymethyl) phenol is prepared by a synthesis which comprises the following steps:

- reaction of the phenol with HBr in organic solvent to obtain (bromomethyl)phenol, and
- reaction of the (bromomethyl) phenol in organic solvent with $AgNO_3$ with formation of (nitroxymethyl)phenol.

The process based on the reaction between (nitroxymethyl) phenol and the acyl chloride of the acetylsalicylic acid shows the following drawbacks:

- the (bromomethyl)phenol obtained in the first synthesis step is a chemically unstable and irritating compound;
- the nitrating agent used in the reaction with (bromomethyl)phenol is a very expensive reactant;
- the (nitroxymethyl)phenol is an unstable compound, which can easily decompose in an uncontrollable way; and it must be purified before the reaction with the acetylsalicylic acid chloride, furtherly increasing the production costs and requiring supplementary units in the production plant.

In conclusion the synthesis of above derivatives, by using the intermediate (nitroxymethyl) phenol, is difficult and expensive to be carried out on an industrial scale.

In PCT Patent EP 00/00353 in the name of the Applicant a

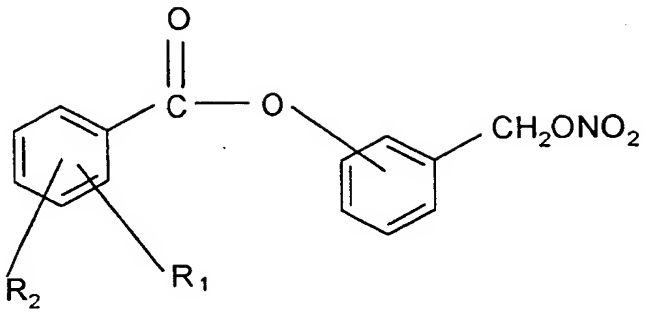
synthesis process of nitroxy derivatives of formula (I) (see hereunder) is described, by submitting to nitration with $AgNO_3$ (hydroxymethyl) phenyl esters of the acetylsalicylic acid, obtained by reacting the acid chloride with hydroxybenzaldehyde and reducing the aldehydic group to primary alcohol. Also this process, as the above mentioned uses silver nitrate as nitrating agent and therefore it is not much advantageous from an industrial point of view. Besides the process global yields are not high.

By using the teaching of the prior art, it is possible to obtain the salicylic acid nitroxyderivatives of formula (I) (see below) by reacting a (hydroxymethyl)phenyl ester of the acetylsalicylic acid with nitrating reactants based on nitric acid. However under the reaction conditions of the prior art the nitric acid produces undesired reactions, such as for example the nitration of aromatic substrata (ref. "Nitration: Methods and Mechanism", 1984 VCH ed., p. 269) and the oxidation of primary alcohols to aldehydes (ref. "Industrial and Laboratory Nitration" 1976 ACS publ., p. 156).

Therefore also said processes of the prior art are unable to solve the problem of the preparation on industrial scale of the nitroxyderivatives of the salicylic acid as above defined.

The need was felt to prepare nitroxy derivatives of (hydroxymethyl)phenyl esters of the acetylsalicylic acid by a process cheaper than those of the prior art both for the nitrating agent used and for the yields, and substantially without the drawbacks of the prior art.

An object of the present invention is a process for obtaining (nitroxymethyl)phenyl esters of the salicylic acid derivatives, compounds having the following formula (I):



(I)

wherein:

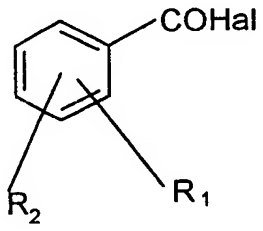
R_1 is the $OCOR_3$ group; wherein R_3 is methyl, ethyl or linear or branched C_3-C_5 alkyl, or the residue of a saturated heterocyclic ring having 5 or 6 atoms, containing hetero-atoms independently selected between O and N;

R_2 is hydrogen, halogen, linear or branched when possible C_1-C_4 alkyl, linear or branched when possible C_1-C_4 alkoxyl; linear or branched when possible C_1-C_4 perfluoroalkyl, for example trifluoromethyl; mono- or di- (C_1-C_4)alkylamino;

preferably in (I) R_1 is acetoxy and is in ortho position with respect to the carboxylic group, R_2 is hydrogen; the oxygen of the ester group is bound to the aromatic ring substituted with the (nitroxy)methylene group in ortho, meta or para position with respect to the (nitroxy)methylene group; preferably the position is the meta one;

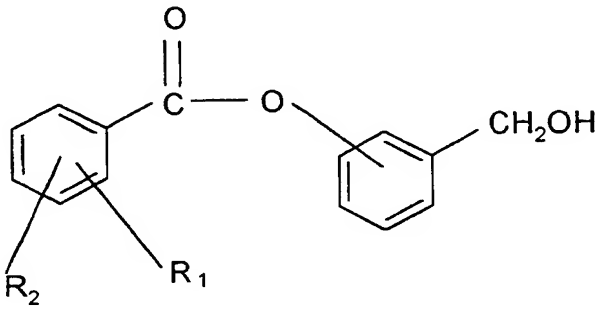
said process comprising the following steps:

a) reaction of a halide of a salicylic acid derivative of formula (I-A):



(I-A)

wherein Hal = Cl, Br, and R_1 and R_2 have the above indicated meaning, with hydroxybenzylalcohol in the presence of a base, in an organic solvent, or in a mixture of water with a miscible or immiscible organic solvent with water, to give the compound (I-B) having the following formula:



(I-B)

wherein R_1 and R_2 are as above defined;

b) nitration of the compound (I-B) in anhydrous conditions, in an inert organic solvent, by a mixture formed by steaming nitric acid with an inorganic acid different from nitric acid or with an organic acid, or with the anhydride of one or two organic acids, to give the nitroxyderivative of formula (I).

c) recovery of the final product by adding water to the organic phase, separating the phases, drying and evaporating the organic phase.

In step a) the base can be an inorganic base, such as for example hydroxides, oxides, carbonates and bicarbonates of alkaline metals (sodium, potassium, lithium); or an organic base, for example a tertiary amine, for example aliphatic, cycloaliphatic, heterocyclic, heterocyclic aromatic, such as triethylamine, diisopropyl-ethylamine, N-methylmorpholine, diazaabicyclooctane, etc.

The organic solvent used in step a) can be an organic solvent miscible with water such as C_1-C_4 aliphatic alcohols, for example methanol, ethanol, isopropanol, n-butanol; or an

organic solvent immiscible with water for example aromatic hydrocarbons such as toluene and xylene, chlorinated organic solvents such as methylene chloride, chlorobenzene, other solvents which can be used are aliphatic esters for example of C_1-C_4 acids with C_1-C_5 alcohols such as for example ethyl acetate and butyl acetate, etc.: aliphatic and cycloaliphatic ketones, such as C_3-C_{12} for example acetone, methylketone, cyclohexanone, etc.

In step a) the reaction is carried out at a temperature in the range -20°C and +50°C, preferably 0°C-20°C, by using, with respect to the hydroxybenzylalcohol moles under reaction, an amount by moles of acid halide (I-A) in a ratio between 1 and 2, preferably between 1.2 and 1.5, and an amount by moles of base between 0.1 and 2, preferably between and 2.

The compound I-B) is recovered from the reaction mixture by addition of water and optionally, when the reaction takes place in an aqueous solvent or in a mixture of water with an hydrosoluble organic solvent, by addition of an organic solvent immiscible with water, such as ethyl acetate or dichloromethane, the phases are separated, the organic phase is dried, evaporated and the product is recovered. If necessary, the compound can be purified by crystallization from solvents such as for example n-hexane, n-heptane, ligroin, toluene, methanol, isopropanol, diisopropylether, etc or their mixtures. Generally the yields are higher than 80%.

In step b) the nitration reaction is carried out at a temperature in the range -20°C and +40°C, preferably from 0°C to 20°C; the used amount by moles of nitric acid is in a ratio between 1 and 6, preferably 1 and 3, with respect to the moles of the hydroxyester (I-B); the amount by moles of organic or inorganic acid different from nitric acid, or of anhydride as above defined, is in a ratio comprised betwenn 0.5 and 6, preferably between 1 and 3 with respect to the moles of the compound (I-B).

The inorganic acid different from nitric acid is for example sulphuric acid; the organic acid is for example methansulphonic acid, trifluoromethansulphonic acid, trifluoroacetic acid, trichloroacetic acid, acetic acid; the organic

acid anhydride is for example acetic anhydride, trifluoromethansulphonic anhydride, trifluoroacetic anhydride, trichloroacetic anhydride, etc., or mixed anhydrides such as for example trifluoroacetic-trifluoromethansulphonic anhydride, etc.

The inert organic solvent used in step b) is a solvent which has boiling point lower than 200°C at atmospheric pressure and it can be a chlorinated solvent, such as for example dichloromethane; or a nitroalkane such as for example nitromethane, or an aliphatic or cycloaliphatic ether such as for example methylterbutylether, tetrahydrofuran, etc.; an ester for example ethyl acetate; or an aliphatic or aromatic nitrile such as for example acetonitrile, benzonitrile.

The solvent volume is not critical, generally the volume is comprised betwen 1 and 20 times with respect to the amount by weight of hydroxyester (I-B) under reaction.

When the nitration in step b) is carried out in the presence of an organic anhydride as above defined, preferably the anhydride is first mixed with the hydroxyester (I-B) and then the resulting mixture is added to the nitric acid solution in the inert organic solvent.

Preferably the used organic anhydride is acetic anhydride.

In step c) it is possible to recrystallize the obtained compound by using solvents such as for example n-hexane, n-heptane, ligroin, methanol, isopropanol or their mixtures.

The following Examples describe the invention without limiting the scope thereof.

EXAMPLE 1a

Preparation of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (compound I-B) in admixture water-organic solvent

3-hydroxymethylphenol (25.25 g, 0.2 moles) is dissolved in a 5% hydroxide sodium solution (160 ml). To the so obtained solution an acetylsalicylic acid chloride solution (40.4 g, 0.2 moles) in dichloromethane (50 ml) is added at room temperature, under stirring. The mixture is maintained at room temperature under stirring for 2 hours and then extracted with dichloromethane (2 x 100 ml). The organic phase is separated,

anhydrified with sodium sulphate and the solvent evaporated under vacuum. The residue is crystallized from a mixture of ethyl acetate and hexane. 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (45.8 g, 0.16 moles, yield 80%) is obtained.

M.P.: 79°-81°C.

^{1}H NMR($CDCl_3$) δ (ppm): 2.29 (s, 3H); 4.71 (s, 2H); 7.07-8.2 (m, aromatics, 8H).

EXAMPLE 1b

Preparation of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (compound I-B) in organic solvent immiscible with water

3-hydroxymethylphenol (10 g, 0.08 moles) is dissolved in toluene (50 ml) containing triethylamine (9.8 g, 0.1 moles). To the so obtained solution an acetylsalicylic acid chloride solution (16 g, 0.08 moles) in toluene (50 ml) is added at a temperature of 5°-10°C under stirring. The mixture is maintained at a temperature in the above mentioned range, under stirring for 2 hours, then poured in water and then extracted with dichloromethane (2 x 100 ml). The organic phase is separated, washed in sequence with a 25% w/v potassium carbonate solution, with water, with a 3% hydrochloric acid solution and lastly with water again, then anhydrified with sodium sulphate and the solvent evaporated under vacuum. The residue is crystallized from isopropanol. 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (45.8 g, 0.16 moles, yield 80%) is obtained.

M.P.: 79°-81°C.

^{1}H NMR($CDCl_3$) δ (ppm): 2.29 (s, 3H); 4.71 (s, 2H); 7.07-8.2 (m, aromatics, 8H).

EXAMPLE 1c

Preparation of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (compound I-B) in organic solvent miscible with water

3-hydroxymethylphenol (10 g, 0.08 moles) is dissolved in acetone (50 ml). In the obtained solution potassium carbonate in powder (22.2 g, 0.16 moles) is suspended. To the suspension

an acetylsalicylic acid chloride solution (16 g, 0.08 moles) in acetone (50 ml) is added at a temperature of 5°-10°C, under stirring. The mixture is maintained at a temperature in the above mentioned range, under stirring, for 2 hours, then filtered and the solvent evaporated under vacuum. The residue is crystallized from isopropanol. 3-hydroxymethylphenyl ester of the 2-acetoxy-benzoic acid (21.0 g, 0.07 moles, yield 91%) is obtained.

M.P.: 79°-81°C.

^{1}H NMR($CDCl_3$) δ (ppm): 2.29 (s, 3H); 4.71 (s, 2H); 7.07-8.2 (m, aromatics, 8H).

EXAMPLE 2

Preparation of 3-nitroxymethylphenyl ester of the 2-acetoxy-benzoic acid by nitration with steaming nitric acid, in the presence of sulphuric acid, of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid.

A solution of steaming nitric acid (3.92 g, 62.2 mmoles, 3 moles with respect to the moles of the hydroxyester I-B) and sulphuric acid 96% (6.10 g, 62.2 mmoles, 3 moles with respect to the moles of the hydroxyester 1-B) in dichloromethane (25 ml) is cooled at 0°C and added in 1 hour, under stirring and in nitrogen atmosphere, with a 3-hydroxymethylphenyl ester solution of the 2-acetoxybenzoic acid (6 g, 20.7 mmoles) in 25 ml of dichloromethane. The mixture is then diluted with dichloromethane (50 ml) and poured into water and ice (100 g). The organic phase is separated, washed with water, anhydrified with sodium sulphate and the solvent evaporated under vacuum. The residue is crystallized from isopropanol obtaining the 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid (5.6 g, 17 mmoles, yield 82%).

M.P.: 61°-62°C.

^{1}H NMR($CDCl_3$) δ (ppm): 2.31 (s, 3H); 5.44 (s, 2H); 7.16-8.22 (m, aromatics, 8H).

EXAMPLES 2a-2f

Example 2 was repeated by varying the moles of nitric acid and of sulphuric acid with respect to the moles of the intermediate 3-hydroxymethylphenyl ester of the 2-

acetoxybenzoic acid (I-B). In the following Table 1 the molar ratios of the used reactants with respect to the compound I-B and the relative per cent ratio between the 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid (I), the 3-(formyl)phenyl ester of the 2-acetoxybenzoic acid (I-B1) are reported, considering, when present, also the starting compound (I-B).

The Table shows that the highest yield is obtained by using the molar ratio nitric acid/compound (I-B) equal to 3 and sulphuric acid/compound (I-B) equal to 1.5.

Table 1

Example	Moles HNO_3/I-B	Eq. H_2SO_4/I-B	Moles H_2SO_4/I-B	Relative Ratio %		
				(I)	(I-B)	(I-B1)
a	2	0	0	5	15	80
b	2	1	0.5	25	0	75
c	1	1	0.5	54	0	46
d	1	0.5	0.25	5	14	55
e	2	2	1	69	0	31
f	3	3	1.5	99	0	1

EXAMPLE 3

Preparation of 3-nitroxymethylphenil ester of the 2-acetoxybenzoic acid by nitration with steaming nitric acid, in the

presence of acetic anhydride, of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid.

A solution of steaming nitric acid (1.44 g, 22.8 mmoles), acetic anhydride, (2.33 g, 22.8 mmoles) in dichloromethane (25 ml) is cooled at 0°C and under stirring added in 1 hour, in nitrogen atmosphere, with a 3-hydroxymethylphenyl ester solution of the 2-acetoxybenzoic acid (6 g, 20.7 mmoles) in 25 ml of dichloromethane. The mixture is heated up to 20°C in one hour and then diluted with dichloromethane (50 ml) and poured into water and ice (100 g). The organic phase is separated, washed with water, anhydrified with sodium sulphate and the solvent evaporated under vacuum. The residue is crystallized from isopropanol and 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid (5.6 g, 17 mmoles, yield 82%) is obtained.

EXAMPLE 4

Preparation of 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid by nitration with steaming nitric acid, in the presence of acetic anhydride, of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (acetic anhydride mixed with hydroxyester).

A solution of steaming nitric acid (1.44 g, 22.8 mmoles), in dichloromethane (25 ml) is cooled at 0°C and added in 1 hour, under stirring and in nitrogen atmosphere, with a solution of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (6 g, 20.7 mmoles) and acetic anhydride (2.33 g, 22.8 mmoles) in 25 ml of dichloromethane. The mixture is heated up to 20°C in one hour and then diluted with dichloromethane (50 ml) and poured into water and ice (100 g). The organic phase is separated, washed with water, anhydrified with sodium shulphate and the solvent evaporated under vacuum. The residue is crystallized from isopropanol to give 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid (6.42 g, 19.5 mmoles, yield 94%).

EXAMPLE 5

Preparation of 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid by nitration with steaming nitric acid, in the presence of methansulphonic acid, of 3-hydroxymethylphenyl

ester of the 2-acetoxybenzoic acid.

A steaming nitric acid solution (1.44 g, 22.8 mmoles) and methansulphonic acid (2.55 g, 22.8 mmoles) in dichloromethane (25 ml) is cooled at 0°C and under stirring added in 1 hour, in nitrogen atmosphere, with a 3-hydroxymethylphenyl ester solution of the 2-acetoxybenzoic acid (6 g, 20.7 mmoles) in 25 ml of dichloromethane. The mixture is diluted with dichloromethane (50 ml) and poured into water and ice (100 g). The organic phase is separated, washed with water, anhydrified with sodium sulphate and the solvent evaporated under vacuum. The residue is crystallized from isopropanol to give 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid (2.73 g, 8.29 mmoles, yield 40%).

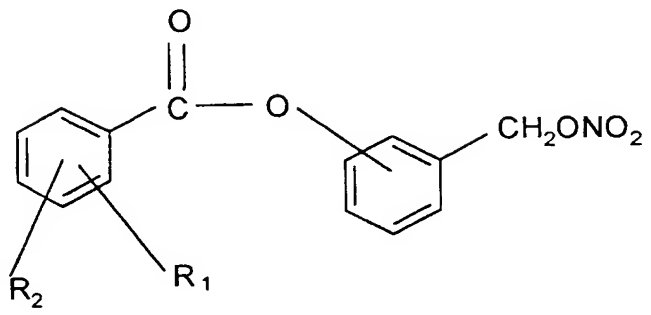
EXAMPLE 6

Preparation of 3-nitroxymethylphenyl ester of 2-acetoxybenzoic acid by nitration with steaming nitric acid, in the presence of acetic anhydride, of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid.

A steaming nitric acid solution (990 mg, 15.2 mmoles), acetic anhydride (1.55 g, 15.2 mmoles) in dichloromethane (25 ml) is cooled at 0°C and, under stirring, added in 1 hour, under nitrogen atmosphere, with a solution of 3-hydroxymethylphenyl ester of the 2-acetoxybenzoic acid (4 g, 13.8 mmoles) in 25 ml of dichloromethane. The mixture is heated in one hour up to 20°C and then diluted with dichloromethane (50 ml) and poured into water and ice (100 g). The organic phase is separated, washed with water, anhydrified with sodium sulphate and the solvent evaporated under vacuum. The residue is crystallized from isopropanol to give 3-nitroxymethylphenyl ester of the 2-acetoxybenzoic acid (4.1 g, 12.28 mmoles, yield 89%).

CLAIMS

1. A process for obtaining compounds of formula (I):



(I)

wherein:

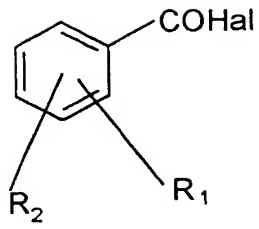
R_1 is the $OCOR_3$ group; wherein R_3 is methyl, ethyl or linear or branched C_3-C_5 alkyl or the residue of a saturated heterocyclic ring having 5 or 6 atoms, containing heteroatoms independently selected between O and N;

R_2 is hydrogen, halogen, linear or branched when possible C_1-C_4 alkyl, linear or branched when possible C_1-C_4 alkoxyl; linear or branched when possible C_1-C_4 perfluoroalkyl; mono- or di- (C_1-C_4) alkylamino;

preferably in (I) R_1 is acetoxy and it is in ortho position with respect to the carboxylic group, R_2 is hydrogen; the oxygen of the ester group is bound to the aromatic ring substituted with the (nitroxy)methylene group in ortho, meta or para position with respect to the (nitroxy)methylene group; preferably the position is the meta one;

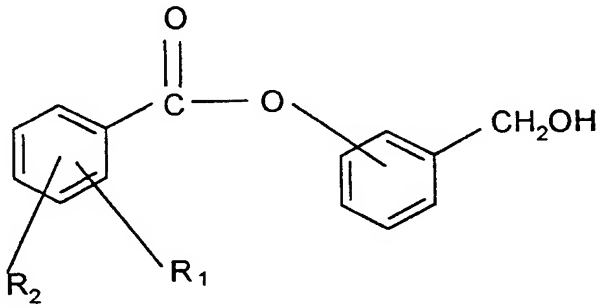
said process comprising the following steps:

a) reaction between an halide of a salicylic acid derivative of formula (I-A)



(I-A)

wherein Hal = Cl, Br, and R_1 and R_2 have the above indicated meaning, with hydroxybenzylalcohol in the presence of a base in an organic solvent, or in a mixture of water with an organic solvent miscible or immiscible with water, to give the compound (I-B) having the following formula:



(I-B)

wherein R_1 and R_2 are as above defined;

b) nitration of the compound (I-B) in anhydrous conditions, in an inert organic solvent, by a mixture formed by steaming nitric acid with an inorganic acid different from nitric acid, or with an organic acid, or with an anhydride of one or two organic acids to give the nitroxy derivative of formula (I).

c) recovery of the final product by adding water to the organic phase, separating the phases, drying and

evaporating the organic phase.

2. A process according to claim 1, wherein in step a) the base is an inorganic or organic base.

3. A process according to claims 1-2, wherein in step a) the organic solvents are C_1-C_4 aliphatic alcohols; aromatic hydrocarbons, aliphatic esters, chlorinated organic solvents, alipahtic and cycloaliphatic ketones.

4. A process according to claims from 1 to 3, wherein in step a) the reaction is carried out at a temperature in the range -20°C and +50°C by using, with respect to the hydroxybenzylalcohol moles under reaction, an amount by moles respectively of acid halide (I-A) in the range between 1 and 2, preferably between 1.2 and 1.5 and an amount by moles of base in the range between 0.1 and 2, preferably between 0.5 and 2.

5. A process according to claim 1, wherein in step b) nitration is carried out at a temperature in the range -20°C and +40°C and the amount by moles of nitric acid is in a ratio between 1 and 6, preferably between 1 and 3, with respect to the moles of the compound (I-B), the amount by moles of inorganic acid different from nitric acid, or of organic acid or of organic anhydride as above defined, is in a ratio comprised beteen 0.5 and 6, preferably between 1 and 3 with respect to the moles of the compound (I-B).

6. A process according to claim 5, wherein nitration is carried out in the presence of an anhydride, which is premixed with the hydroxyester (I-B) and the resulting mixture added to the nitric acid solution in the inert organic solvent.

7. A process according to claim 6, wherein anhydride is acetic anhydride.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/05722

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C203/04 C07C201/02 C07C67/14 C07C69/90

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 95 09831 A (NICOX LTD) 13 April 1995 (1995-04-13) claims 15,16	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
9 November 2000	22/11/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bonnevalle, E

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